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Autistic Disorder and Phospholipids: A Review

Christine M. Brown (cmbrown@swin.edu.au)*

Faculty of Life and Social Sciences

Swinburne University of Technology, Hawthorn VIC 3122 Australia

David W. Austin (daustin@swin.edu.au)

Faculty of Life and Social Sciences

Swinburne University of Technology, Hawthorn VIC 3122 Australia

*Corresponding Author

Abstract

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3 Deregulated phospholipid metabolism has been proposed as an underlying biological component
4 of neurodevelopmental disorders such as Autistic Disorder and ADHD. The purpose of this
5 review is to provide an overview of fatty acid and phospholipid metabolism and the evidence for
6 phospholipid dysregulation with reference to the membrane hypothesis of schizophrenia. While
7 there is evidence that phospholipid metabolism is at least impaired in individuals with AD, it has
8 not been established whether phospholipid metabolism is implicated in causal, mechanistic or
9 epiphenomenological models. More research is needed to ascertain whether breastfeeding, and
10 specifically, the administration of colostrum or an adequate substitute can play a preventative
11 role by supplying the neonate with EFAs at a critical juncture in their development. In regard to
12 treatment, further clinical trials of EFA supplementation are essential to, at worst, eliminate the
13 possibility of the efficacy of EFAs in reducing AD symptomatology and at best, determine
14 whether supplementation can serve as a cost-effective and readily available intervention.

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Introduction

Autistic Disorder (AD) is a lifelong neurodevelopmental disorder that has been growing in prevalence over several decades (1). AD is now a more prevalent childhood disorder than Type 1 diabetes, Down Syndrome and childhood cancer combined (2). In the UK, 1% of children aged between 5- and 9- years of age have an existing diagnosis on the autistic spectrum and for every three cases that are diagnosed, there may be a further two cases that remain undiagnosed (3). These figures represent a twelve-fold increase in AD over the last 30 years (3). In Australia, prevalence is established at 1 in 160 children (4) however, this figure is based on data from 2003/4 and therefore may underestimate true prevalence. Although there is no general agreement as to the reason(s) for this continuing increase in prevalence, with the number of children diagnosed with AD growing, research into the disorder gathers even more urgency and the burden on families, health, education and welfare services ever greater.

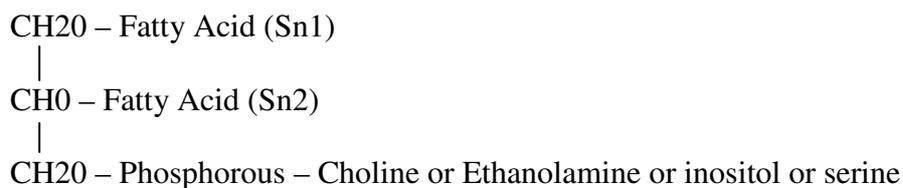
For much of its history, AD has been considered a discrete psychological disorder and largely managed with behavioural interventions. However, many studies have outlined the dimensionality of AD in regard to its comorbidity with other neurodevelopmental disorders such as ADHD, Dyslexia, Dyspraxia (5) and epilepsy (6). In addition to this, the facts that all of the aforementioned disorders affect a disproportionate number of males than females and that there is a strong familial association has led to a re-conceptualisation of these disorders (5). A new proposition is that there may be an underlying biological component that is modified by an individual's genetic constitution and exposure to environmental factors (7). Researchers are now theorising that one of the underlying biological components in all these neurodevelopmental disorders involves deregulated phospholipid metabolism (5, 8) (9).

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Phospholipids, fatty acids and metabolism

Phospholipids are major structural components of neuronal cell membranes and are comprised of a glycerol three-carbon atom backbone, with a phosphorous in the third position and fatty acids of many different types attached to the first two carbons. The synthesis and breakdown of phospholipids are involved in the growth and restructuring of synaptic connections (10).

Figure 1: Phospholipid structure



Fatty acids are comprised of an organic acid group known as carboxylic acid and a long chain (aliphatic) tail of carbon and hydrogen. The aliphatic tail of a fatty acid can lack double carbon bonds or contain up to six, and the number of double bonds determines the saturation of the fatty acid. Thus, an absence of carbon bonds allows the fatty acid to be saturated with hydrogen and creates a straight, inflexible structure (a saturated fatty acid) whilst one carbon bond creates a fatty acid which is curved (monosaturated) and multiple double bonds create flexible ‘U’ shaped structures known as Polyunsaturated Fatty Acids (PUFAs). PUFAs are incorporated into the nerve cell membranes of the brain and retina and contribute to the functional maturation of the Central Nervous System (11).

1 Fatty acids are required for phospholipid metabolism and both saturated and monosaturated
 2 fatty acids can be synthesized within the body. However PUFAs are classed as Essential Fatty
 3 Acids (EFAs) because they cannot be synthesized by the body endogenously and must be
 4 provided by the diet (12). Fatty acid metabolism begins with two precursor fatty acids: LA(18:2
 5 n-6) an Omega-6 fatty acid, and ALA(18:3 n-3) an Omega-3 fatty acid. Fatty Acid metabolism
 6 involves an elongation and de-saturation process which means that at each iteration, the aliphatic
 7 tail of the PUFAs become longer and collects more carbon double bonds thus becoming more
 8 unsaturated. The PUFAs with the most highly unsaturated tails are EPA (20:5, n-3), DPA(22:5,
 9 n-3), DPA(22:5n-3) and DHA(22:6, n-3) and they are known as Highly Unsaturated Fatty Acids
 10 (HUFAs).

11

12 Table 1. Elongation and desaturation pathways for Omega-6 and Omega-3 PUFAs

13

Omega-6	Code	Enzymes	Omega-3	Code
Linoleic (LA)	18:2 (n-6)	Delta 6- desaturase	Alpha-Linolenic (ALA)	18:3 (n-3)
γ -Linolenic (GLA)	18:3 (n-6)	Elongase	Octadectetraenoic	18:4 (n-3)
Dihomogamma- linolenic (DGLA)	20:3 (n-6)	Delta-5- desaturase	Eicosatetraenoic	20:4 (n-3)
Arachidonic (AA) aka (ARA)	20:4 (n-6)	Elongase	Eicosapentaenoic (EPA)	20:5 (n-3)
Adrenic	22:4 (n-6)	Elongase	Docosapentaenoic (DPA)	22:5 (n-3)
Docosapentaenoic (DPA)	22:5 (n-6)	Elongase, delta-6- desaturase, beta- oxidation	Docosahexaenoic (DHA)	22:6 (n-3)

14

15

1 The brain phospholipids are exceptionally rich in HUFAs (12); (10) and in contrast to other
2 bodily tissue, a unique feature of neurons is the smaller amounts of the precursors LA (18:2, n-6)
3 and ALA (18:3, n-3) and the higher amounts of their metabolites: AA(20:4, n-6) and DHA(22:6,
4 n-3) (10);(13), (14) The two major PUFAs in all vertebrates are AA (20:4, n-6) and DHA
5 (11)and account for 20% of the dry brain weight (12) (15). Also present in phospholipids are
6 DGLA(20:3, n-6), Adrenic Acid(22:5, n-6), EPA(20:5, n-3) and DPA(22:5, n-3) but they are not
7 as prolific as AA(20:4, n-6) and DHA (10); (13). DHA is known to be involved in cell signaling
8 and cell proliferation (16)) and has an important structural role in the brain (17) whilst AA is
9 crucial for brain growth. EPA(20:5, n-3) has no structural role, but it is considered vital for the
10 regulation of brain function (17).

11
12 Phospholipases are enzymes that break down phospholipids and particular interest is taken in the
13 phospholipases A2 (PLA2) enzymes which are upstream regulators of many inflammatory
14 processes. PLA2 recognizes the Sn2 bond in phospholipids and catalytically hydrolyzes the bond
15 releasing AA(20:4, n-6), EPA(20:5, n-3) and DHA(22:6, n-3) (18).AA is then modified in active
16 compounds called eicosanoids (prostaglandins, leukotrienes and thromboxanes) which are local
17 hormones that participate in a number of physiological as well as pathophysiological conditions
18 such as the activation of immune cells, platelet aggregation and parturition initiation (19). EPA
19 and DHA are metabolized to resolvins and protectins that have important roles in the resolution
20 of inflammation (18).

21
22 Phospholipids are a unique intersection of the environment and genes as the final structure of
23 each phospholipid molecule depends on an interaction between genetic and environmental
24 factors (20). That is, the enzymes involved in the synthesis and breakdown of phospholipids are

1 under genetic control, but the key EFAs of neuronal phospholipids must come from the diet. As
2 the EFAs cannot be synthesized de novo, if EFAs are unavailable they will be replaced by non-
3 essential fatty acids, such as saturated fats, thus changing the phospholipid structure (10). For
4 example, during dietary deprivation of ALA(18:3 n-3), DHA(22:6, n-3) is replaced by
5 DPA(22:5, n-6) in the retina and brain of animals (21). As this fatty acid is the most like DHA
6 this seems to suggest the existence of a compensatory mechanism (21).

7
8 A disruption of membrane phospholipid metabolism was originally proposed by (22) as the
9 possible etiological basis of schizophrenia and is known as the membrane hypothesis of
10 schizophrenia. The concept proposes that brain phospholipid metabolism is altered because of an
11 increased rate of loss of DGLA(20:3, n-6), EPA(20:5, n-3), AA(20:4, n-6) and DHA(22:6, n-3)
12 from the Sn2 position of phospholipids. This loss leads to changes in the functioning of the
13 membrane-associated proteins and of the cell signaling systems. One explanation for this is
14 thought to be overactivity of one or more of the PLA2 group of enzymes which remove these
15 EFAs from the Sn2 position.

16

17 The evidence put forward for the membrane hypothesis of schizophrenia is as follows:

18

- 19 1. Increased circulating levels of PLA2 enzymes in the bloodstream (23) (24, 25).
- 20 2. Reduced levels of AA(20:4, n-6) and DHA(22:6, n-3) in red cell membrane
21 phospholipids (26, 27) (28, 29), perhaps due to oxidative stress (30).
- 22 3. MRI indicates an increased rate of phospholipid breakdown in the brain of unmedicated
23 schizophrenics (31) (32).

- 1 4. A diagnosis of schizophrenia is associated with a reduced flushing response to oral or
2 topical niacin indicating that the amount of available AA(20:4, n-6) is reduced (33)
- 3 5. Reduced ERG response to light stimulus (34-36) indicating reduced DHA(22:6, n-3)
4 availability (10, 35)
- 5 6. Two different genetic abnormalities found on chromosome 1 in the vicinity of the gene
6 for PLA2 (37).
- 7 7. Clozapine raises the red cell phospholipid AA and DHA levels in schizophrenic patients
8 (38) and may account for some of the therapeutic effects (10)
- 9 8. Resistance to arthritis and other inflammatory diseases, resistance to pain and
10 improvement in psychosis which frequently occurs in response to fever (22, 39, 40).

11
12 With evidence mounting that irregular phospholipid metabolism was, at least, concomitant with
13 schizophrenia, research commenced into other neurodevelopmental disorders with the finding
14 that fatty acid deficiencies are also over-represented in Attention Deficit Hyperactivity Disorder
15 (ADHD), Depression, Pervasive Developmental Disorder, Developmental Coordination Disorder
16 and Epilepsy (41) (42); (12, 43).

17
18 Further, dysregulated lipid metabolism is now accepted as a pathogenic factor in many
19 neurological disorders such as bipolar disorder and neurodegenerative diseases such as
20 Alzheimer's, Parkinson's, Niemann-Pick and Huntington diseases (18) Altered lipid metabolism
21 is also believed to be a key event which contributes to Central Nervous System (CNS) injuries
22 such as stroke (18).

23

1 Research into phospholipids in AD is in its infancy and began with the observation that many
2 children with AD have visible signs of fatty acid deficiencies such as excessive thirst, frequent
3 urination, keratosis pilaris on the upper arms or upper thighs, dandruff, and atopic tendencies
4 (43).

5

6 **The evidence for a phospholipid pathogenic component in autism spectrum disorder.**

7

8 *1. Increased circulating levels of PLA2 enzymes in the bloodstream*

9

10 Bell, MacKinlay, Dick, MacDonald, Boyle and Glen (43) identified significantly increased red
11 blood cell type IV PLA2 activity in patients with regressive autism, classical autism and
12 Aspergers syndrome which is consistent with previous findings of elevated PLA2 in
13 schizophrenia, depression, bipolar disorder and dyslexia (44). An unexpected finding was that
14 the HUFA composition of the regressive autism group reduced dramatically by between 60-82%
15 following six weeks of storage at -20 degrees C. This unexpected loss of red blood cell PUFAs
16 was also found in a study of schizophrenic patients (45). At -20 degrees C, the decay rates of
17 schizophrenic patients' red blood cell PUFAs were nearly twice that of non-patient control
18 participants. Both studies theorized that elevated levels of PLA2 activity may account for the
19 increased degradation (43, 45) although Bell et al also considered a possibility of increased lipid
20 peroxidation in the affected sample .

21

22

23 *2. Reduced levels of AA and DHA in red cell membrane phospholipids*

24

1 A study comparing plasma fatty acid levels of children with AD and children with mental
2 retardation and no autism diagnosis found that DHA(22:6, n-3) levels were reduced by 23% in
3 autistic children (12). AA(20:4, n-6) levels were also lower (but not significantly) and the total
4 PUFA levels were reduced by about 20% in the total plasma of children with autism (12). A
5 significant increase in the Omega 6/Omega 3 ratio values in children with AD was found. There
6 was also a tendency to reduced levels of EPA(20:5, n-3) but not significantly. It was noted that
7 the children with mental retardation may not serve as a true control given that they also may have
8 fatty acid deficiencies so the differences between groups may have been reduced (12). In another
9 study, significantly lower levels of AA were found in patients with regressive autism compared
10 to controls (43).

11

12 A case study of an 8-year-old male found reduced levels of DHA and EPA, despite a normal
13 blood level of their precursor, ALA(18:3 n-3). Omega-6 fatty acids were at normal levels (46).

14

15 Bu et al (47) were not able to replicate the findings of Bell et al (43) although a few alterations of
16 red blood cell membrane fatty acids were found in regressive autistic children. Bu et al did not
17 find an increased ARA(20:4, n-6)/EPA(20:5, n-3) ratio in children with classic or regressive
18 autism. Whilst EPA levels in both classic and regressive autistic groups had wider variations
19 compared to the children with developmental disabilities and the neurotypical control group, the
20 variation was not significant. However, Bu et al also reported that two PUFAs, eicosenoic acid
21 and erucic acid, were elevated in children with regressive autism compared to the neurotypical
22 control group. As eicosenoic acid is a saturated fatty acid, the acid in question must be, in fact,
23 eicosadienoic acid (20:2, n-6). Erucic acid (22:1, n-9) is a monounsaturated acid so the elevated
24 level of erucic acid (22:1, n-9) should not be of significance in regard to the membrane

1 phospholipid hypothesis. A significantly higher level of eicosadienoic acid (20:2, n-6) was found
2 in children with regressive autism when compared to the group of children with early onset
3 autism. Bu et al did not find any evidence that Omega-3 fatty acids were decreased in children
4 with AD.

5

6 A larger study of 153 cases of autism and 97 general population controls (48) found an overall
7 trend for those with an autism diagnosis to have lower DHA(22:6, n-3) levels, however lipid
8 compositions varied sufficiently to overlap with the distributions in the control group.

9 Interestingly, significantly lower levels of AA(20:4, n-6) were found, but only in the females
10 with autism compared with the female controls.

11

12 3. *MRI*

13

14 No MRI studies investigating phospholipid metabolism have been conducted with individuals
15 with an autism diagnosis.

16

17 4. *Niacin response*

18

19 Puri and Singh (49) found no significant difference between the mean volumetric niacin response
20 in patients with autism and the mean volumetric niacin response in the control group. They
21 concluded that the fatty acid abnormalities in autism are likely to differ from those that occur in
22 schizophrenia.

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24 5. *Reduced ERG response*

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Reduced ERG b-wave amplitude was found in 48% of individuals with AD (50) and four out of six first degree relatives (51). ERG responses were altered in a group of autistic children when compared with a normal reference range of responses and the alterations positively correlated with the clinical severity of the autism (52).

6. Genetic abnormalities on the PLA2 gene

One case study has reported a genetic site linked to autism on chromosome 8q22 is in the proximity of the gene for secretory soluble PLA2 (53) (54). Given the important role the PLA2 enzyme has in hydrolyzing the sn-2 fatty acids in phospholipids it is theorized that this enzyme may have an important role in the etiology of autism (55).

7. Clozapine

A single case study of long-term treatment of autism in an adult male, showed that over a five-year treatment period with Clozapine, there was a marked improvement in levels of aggressiveness and social interaction (56). No data exists in regard to the effect of Clozapine on red cell phospholipid PUFA levels in AD, but the possibility exists that some of the improvement in symptomatology may be due to changes in PUFA levels after administration of Clozapine as per the effect in those with schizophrenia reported in Horrobin (10)

8. Pain and fever response

1 A study of pain reactivity in children with autistic disorder, whilst based on parent report, found
2 abnormally low levels of pain reactivity when compared with non-autistic children when
3 matched for age, sex and socio-economic level (57).

4

5 Curren et al (58) conducted a study in response to the anecdotal evidence of AD symptom
6 improvement during fever. When a child's temperature was over or equal to 38.0 degrees C,
7 fewer aberrant behaviours were found on the domains of irritability, hyperactivity, stereotypy
8 and inappropriate speech.

9

10 Currently, more investigation is required in order to fully understand any possible etiological
11 role of phospholipids in AD. Nevertheless, there appears enough evidence to suggest that fatty
12 acid disruptions or deficiencies are at least a predictable biological presence in AD and, as such,
13 warrant urgent and detailed investigation. Horrobin (10) proposed that increasing the availability
14 of EFAs in the diet would improve symptoms in schizophrenia, however those of the male sex
15 and having an excess of oxidants would reduce the rate of synthesis and incorporation into
16 phospholipids.

17

18

19 **Does an increased availability of EFAs attenuate AD symptomatology?**

20

21 Johnson and Hollander (59) supplemented an 11-year-old boy with a history of autism with
22 fish oils containing EPA which was increased over a period of four weeks to 540mg per day.
23 Both his parents and clinician reported a complete resolution of anxiety and agitation after a

1 week on that dosage and improvements continued for eight months of follow-up. A significant
2 improvement was noted in the patient's quality of life.

3
4 Amminger et al., (60) gave 1.5g per day of Omega-3 EFAs (.84g EPA, .7 DHA) to seven autistic
5 males (5-17 years) over six weeks. A blinded placebo condition (n = 6) received coconut oil.
6 Children in the Omega-3 condition were found to improve on measures of hyperactivity and
7 stereotypy, each with a large effect size. A non-significant trend towards improvement on
8 hyperactivity was also found. This result is particularly impressive given the short period of
9 supplementation and the very low power of the analyses due to the small sample size. It remains
10 somewhat curious, however, that the researchers chose to use a lipid (coconut oil) as a placebo as
11 it would be reasonable to speculate that such a material would be unlikely to have a purely
12 neutral effect on the subjects' fatty acid metabolism.

13
14 Meguid et al (15) analysed the plasma PUFA levels of 30 autistic children and found that LA,
15 DHA, LNA and AA levels were all significantly lower in the autistic children compared with the
16 control group (n = 30). However the mean ratio of AA/DHA was significantly higher in autistic
17 children compared with the control group. Over a three-month period the clinical group was
18 supplemented with Omega-3 and Omega-6 fatty acids (60 mg DHA, 12mg GLA, 13mg EPA and
19 5 mg AA) and Vitamin E. Sixty-six percent showed clinical and biochemical improvement. From
20 blood analyses, the supplemented group showed elevated levels of DHA and LA.

21
22 Politi et al (61) studied the effects of Omega-3 (0.93 g EPA and DHA) supplementation in an
23 open label study of 19 young adults (18-40 years old) with severe autism (CARS >40) over a
24 period of six weeks. During this period, the researchers also administered 5 mg of Vitamin E to

1 minimize lipid peroxidation. Behaviour was rated using the Rossago Behavioural Checklist and
2 the inter-rater reliability of caregivers was established at or above 90% at baseline. Both problem
3 frequency and average severity scores were obtained at pre-treatment, during- treatment and
4 post-treatment phases. The clinical group, all residents at a Community Centre for individuals
5 with autism, showed no improvements in the weekly average frequency of problematic events.
6 And, according to the researchers, the fact that the severity of symptoms worsened between the
7 pre-treatment period and the treatment period indicates that their results “fail to convincingly
8 demonstrate a beneficial effect of Omega-3 FA supplementation in a group of young adults with
9 severe autism” (p. 684). However, an examination of the average severity scores shows that in
10 the post-treatment phase, all participants are consistently scoring under their baseline. Given that
11 FA supplementation may take up to three months to substantially influence FA deficiencies (17),
12 it may not be appropriate to look for behavioural change immediately upon the institution of a
13 supplementation regime.

14

15 **Is the rate of EFA synthesis sex dependent in AD?**

16

17 In Dyslexia, Dyspraxia and Attentional Disorders without hyperactivity, twice as many males as
18 females are diagnosed (62). For the more disruptive forms of ADHD and AD the ratio is closer to
19 5:1 (62). It is estimated that females, in comparison to males, metabolise fatty acids at a rate of
20 4:1 (63) seemingly due to the fact that testosterone can inhibit fatty acid synthesis (64).
21 Oestrogen appears to attenuate fatty acid metabolism issues and the relative lack of oestrogen in
22 males make them more vulnerable than females to deficiencies in HUFAs (62). Being male is a
23 well-established risk factor for AD (65).

24

1 Wiest et al (48) theorized that the lower AA(20:4, n-6) concentrations in the autistic females may
2 be due to the differences in how autism arises in males and females or due to dietary factors. It
3 would be pertinent to explore the role of oestrogen in AA metabolism to shed further light on this
4 finding.

5

6 **Oxidative stress and AD**

7

8 Lipid peroxidation is increased in the plasma of children with autism when compared with their
9 neurotypical siblings (55). Oxidative stress markers such as reduced levels of glutathione,
10 decreased catalase, abnormal iron and copper levels and increased nitric oxide, have all been
11 found in individuals with an AD diagnosis (55). A review of oxidative stress in psychiatric
12 disorders found evidence for increased oxidative stress in disorders including autism, mental
13 retardation, Rett's disorder, ADHD and schizophrenia (66). Oxidative stress is associated with
14 increased lipid peroxidation as PUFAs are particularly vulnerable to peroxidation by oxyradicals
15 (66).

16

17 **Fatty acid intake and neurodevelopment**

18

19 Individuals with schizophrenia are significantly less likely to have been breastfed than controls
20 (67, 68). The protective effect of breastfeeding may be due to breast milk being a rich source of
21 DGLA, AA, EPA and DHA which may attenuate any adverse consequences of impaired fatty
22 acid synthesis (10). As infants, especially pre-term neonates, are not able to convert dietary LA
23 and ALA precursors at an adequate rate to the EFAs important in brain development (69, 70), it
24 is crucial that preformed DHA and EPA are supplied by diet.

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Prenatally, an increase in Omega-3 rich seafood in the maternal diet during pregnancy has been found to be correlated with optimum outcomes for prosocial behaviour, fine motor, communication and social development scores in children aged from 6 months to 3.5 years of age (71). A study of postnatal EFA supplementation found that premature infant girls supplemented with a high level of DHA(22:6, n-3) performed better at 18 months of age on the Mental Development Index of the Bayley Scales of Infant Development than their non-supplemented peers (72).

10 The importance of EFAs to neurodevelopment is highlighted by the findings of Salem, Litman,
11 Kim and Gawrisch (2001) who demonstrated that when an adult mammal consumes a diet low in
12 DHA(22:6, n-3) and its Omega-3 precursors, the DHA levels in the nervous system is much less
13 altered than are other DHA levels in other organs. The implication being that once neural
14 development has occurred, DHA is “tenaciously retained” (16) p.945. In contrast, animal studies
15 have shown that when Omega-3 fat sources are inadequate during early neural development, then
16 levels of brain and retinal DHA decline (16). This points to the potential for a critical window
17 when EFA status needs to be consolidated to ensure adequate levels in the infant.

18

19 **Is a lack of breastfeeding a risk factor for AD?**

20

21 Schultz et al. (73) surveyed 861 parents of children with AD and 123 parents of children without
22 AD, and found that the children with AD were significantly less likely to have been breastfed.
23 The absence of breastfeeding significantly increased the odds of a later AD diagnosis (OR 2.48,
24 95% CI 1.42, 4.35). The apparent link between AD and breastfeeding was first cogently

1 addressed by Tanoue and Oda (74), who found that a significant number of infants subsequently
2 diagnosed with an AD had been weaned within one week of the commencement of breastfeeding
3 with the duration of breastfeeding proposed as a protective factor. Similarly, the odds of being
4 diagnosed with AD also reduced with the duration of breastfeeding in the Schultz et al study, but
5 not significantly. One major limitation of both of these studies is that colostrum intake was not
6 accounted for as colostrum contains twice the PUFAs as transitional and mature milk (75). At
7 this stage, only in animal research is the importance of early fatty acid consumption in the form
8 of colostrum acknowledged and accepted. A study of neonatal calves found that delaying their
9 colostrum intake by just 24 hours impaired their fatty acid, carotene, retinol and alpha-tocopherol
10 status (76) at least for the first week of life.

11

12

13 **Conclusion**

14

15 A review of the literature suggests that there is compelling evidence that phospholipid
16 metabolism is at least impaired in individuals with AD. However, at this stage, it has not been
17 established whether phospholipid metabolism is implicated in causal, mechanistic or
18 epiphenomenological models. More research is needed to ascertain whether breastfeeding, and
19 specifically, the administration of colostrum or an adequate substitute can play a preventative
20 role by supplying the neonate with EFAs at a critical juncture in their development.

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22 In regard to treatment, further clinical trials of EFA supplementation are essential to, at worst,
23 eliminate the possibility of the efficacy of EFAs in reducing AD symptomatology and at best,
24 determine whether supplementation can serve as a cost-effective and readily available

1 intervention. If so, it is critical to determine which EFAs are most effective and in what ratios.

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3 New non-invasive tests such as the measurement of volatiles in breath (77) need to be rigorously

4 applied to investigate the possibility of establishing a reliable biological diagnostic determinant

5 of AD.

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Tables

Table 1. Elongation and desaturation pathways for Omega-6 and Omega-3 PUFAs

Omega-6	Code	Enzymes	Omega-3	Code
Linoleic (LA)	18:2 (n-6)	Delta 6- desaturase	Alpha-Linolenic (ALA)	18:3 (n-3)
γ -Linolenic (GLA)	18:3 (n-6)	Elongase	Octadectetraenoic	18:4 (n-3)
Dihomogamma- linolenic (DGLA)	20:3 (n-6)	Delta-5- desaturase	Eicosatetraenoic	20:4 (n-3)
Arachidonic (AA) aka (ARA)	20:4 (n-6)	Elongase	Eicosapentaenoic (EPA)	20:5 (n-3)
Adrenic	22:4 (n-6)	Elongase	Docosapentaenoic (DPA)	22:5 (n-3)
Docosapentaenoic (DPA)	22:5 (n-6)	Elongase, delta-6- desaturase, beta- oxidation	Docosahexaenoic (DHA)	22:6 (n-3)

1

Figures

2 Figure 1: Phospholipid structure

3

4 CH₂O – Fatty Acid (Sn1)

5 |

6 CH – Fatty Acid (Sn2)

7 |

8 CH₂O – Phosphorous – Choline or Ethanolamine or inositol or serine

9